(5) The condition of the cerebrospinal fluid a year after treatment is a fairly reliable indicator of whether or not further treatment will be needed.

(6) The most important and reliable item in this connexion is the cell count. If it is normal, then probably all will be well ; if it is still raised it is a danger signal, and the giving of further treatment should be considered.

(7) The behaviour of the cerebrospinal fluid after malaria therapy is so comparatively regular that it is a wise precaution to check any unexpected findings.

(8) The serial testing of the cerebrospinal fluid implies keeping the patient under prolonged supervision. To implement this satisfactorily entails having an adequate follow-up organization.

(9) For the follow-up to be really satisfactory, the services of a suitable social worker and adequate clerical assistance are essential.

(10) A good follow-up helps not only the patient but also the doctor, because it enables him to assess his results more accurately.

REFERENCE

Dattner, B., Thomas, E.W., and Wexler, G. (1944) *Amer. J. Syph.* **28**, 265.

DISCUSSION ON THE PRECEDING PAPERS

Dr. **G. L. M. McElligott** (the President) said that the lesson of the most interesting papers by Drs. Nicol and Whelen seemed to be "more lumbar punctures and yet more lumbar punctures". Those members who had been in the armed Forces during the past few years would all agree how very refreshing it was to be able to order patients into hospitals for investigation of the cerebrospinal fluid. Unfortunately, it was difficult to do this in civil practice, owing to the shortage of hospital beds. Members who had been in the armed Forces had discovered also how relatively common was asymptomatic neurosyphilis. Some of the patients were young men in their early twenties. He believed that in some of them the infection was possibly congenital. By the time that symptoms or signs developed the patients would probably be in the thirties and, because by that time risks of infection would probably be admitted, the true origin of the infection would be missed. In such cases positive cerebrospinal fluid reactions often reverted to negative with a minimum of treatment. When the patients were treated with trivalent arsenical compounds and bismuth their cerebrospinal fluid reactions were usually negative at the end of one course of treatment. Whether or not the cerebrospinal fluid reactions remained negative, he was unable to say ; the recent war did not last long enough for these observations to be made. He understood that Dr. Nicol had suggested that if a patient had not relapsed after a year then he was pretty certain to be all right.

Dr. **Nicol** said that that was not correct. He had said that if a patient relapsed, sero-relapse might come on at any time, not necessarily within a year, but that all such cases would require further treatment. If at the end of a year a patient showed a strongly positive reaction he should be re-treated.

Dr. **McElligott** (continuing) said that the conclusion seemed to have been that if patients defaulted from treatment they were safe because their cerebrospinal fluid reactions were negative. Could one safely draw such a conclusion ?

Dr. **Nicol** said that all patients should have the cerebrospinal fluid tested. He assumed that in those patients who had not been tested, but who were working well three or four years afterwards, the probability was that the reactions were negative.

Dr. **T. E. Osmond** wished to be the first to express his thanks to the authors for their admirable papers. Their results were so well documented that they might fairly be "taken as gospel". Dr. Whelen had pointed out that of 246 patients who had two consecutive negative findings in the cerebrospinal fluid only one had relapsed (presumably at the end of 6-12 months). In other words, the outlook for general paralysis of the insane was very much better than it was years ago ; it might almost be said to be good. He supposed that the series about which they had heard that afternoon was the best and most successful ever reported on in Great Britain or, probably, anywhere else. Speaking as a pathologist, he was naturally particularly interested in the cerebrospinal fluid examination, and he thought that a great advance had been made by the authors in showing that the cerebrospinal fluid test was the thing that mattered and that there was no need to worry about the clinical side. The result of the cerebrospinal fluid test was something by which one could be guided. If the reaction was negative one could say that the outlook was good.

Post-lumbar-puncture headache was a recurrent problem. Some doctors seemed to have no trouble with their patients in this respect. He wondered how many people used the Dattner needle. The number of patients who had headaches was less when this needle was used than when needles of larger bore were employed.

With regard to intolerance to tryparsamide, he could bear out what Dr. Nicol had said. He wondered whether or not anybody present had treated such cases with BAL (2'3-dimercapto-propanyl) ; he thought that it would be well worth trying.

The only other thing which he had to say was that it was no secret that Dr. Nicol and Dr. Whelen were now using penicillin in connexion with their malaria therapy. If penicillin gave results as good as or better than did tryparsamide combined with malaria, its use was likely to save a good deal of trouble, owing to the absence of toxic effects. He thought that penicillin plus malaria probably might be the answer to the problem.

Dr. **W. V. Macfarlane** endorsed remarks which had been made about post-lumbar-puncture headache. In his clinic in Newcastle they had carried out about 900 lumbar punctures in 1945, and, except in a few cases, such as paraplegia, necessitating the patients' admission to hospital, all lumbar punctures were performed in the out-patient department. The incidence of post-lumbar-puncture headache was approximately between 2 and 4 per cent. He considered that a great deal depended upon the speed at which the fluid was drawn off. In his clinic the patient always lay in a supine position for one hour after the lumbar puncture had been performed, but he doubted the benefit of this procedure. The preceding remarks applied to male and female patients.

With reference to penicillin treatment in neurosyphilis, his clinic had started about a year ago to give a total of 4 mega units (initial dose 10,000 units, gradually increasing to 40,000 units per injection), the injections being given at three-hourly intervals over a period of approximately 14 days. Between 40 and 50 patients had been treated thus, and almost all of them tolerated the injections extremely well. Recently his clinic had begun to use a penicillin-oil-wax preparation. The immediate results appeared to have a direct bearing on the duration of clinical neurosyphilis, but those patients who showed a clinical picture of short duration would appear to have benefited more than did patients presenting a history of illness of a much longer duration. He could recall one patient suffering from general paralysis of the insane, the onset being of recent duration, who showed an excellent result after treatment with penicillin. The patient felt very much better, and the cell count, together with the globulin, returned to within normal limits within a period of 6 months. The speaker, however, took the advice of Prof. Stokes in re-admitting this patient after approximately 4 months' interval for a repetition of the course of penicillin.

Dr. Macfarlane was interested to know whether or not any supplementary treatment to penicillin should be given in neurosyphilis. Judging from the return of the cell count and globulin content to within normal limits within a period of 6 months, the result could be regarded as satisfactory, but the great majority of patients very often failed to show any marked reduction of the Wassermann titre in the spinal fluid. The possibility of combining penicillin with hypertherm treatment had been considered.

BAL had been tried in one case of dermatitis due to a trivalent arsenical preparation, and the initial result was most encouraging, but as soon as BAL therapy was stopped the dermatitis recurred ; 48 hours after commencement of BAL administration, purpura of both legs developed and, after a further interval of 24 hours, thrombophlebitis of the left leg appeared. Both complications disappeared after approximately one week.

Dr. **D. I. Williams** said that it was always stimulating to hear papers so well documented as those which had been read to the Society that afternoon. He was inclined to join issue with the President on what he had said about asymptomatic congenital syphilis. Many patients with secondary syphilis had changes in the cerebrospinal fluid, and these changes could be detected long before any signs of neurosyphilis showed themselves. The cases quoted by the President, he thought, were more likely to have been acquired syphilis.

References were made in Dattner's book on neurosyphilis to the question of post-lumbar-puncture headaches, and evidence was quoted in that book (Dattner, Thomas and Wexler) (also in an excerpt in *The Journal of Venereal Disease Information* early in 1945) suggesting that headaches could be avoided if patients, after lumbar puncture, were not put to bed at all but got up immediately and kept on their feet. This plan he had adopted in the Army and no cases of post-lumbar-puncture headache were seen. Whether needles of Dattner's pattern or other needles were used made no difference as long as the patient was not put to bed.

So far as BAL was concerned, he had not seen any reports of its use with tryparsamide. He had not heard of anybody getting phlebitis as a result of BAL administration or of being particularly exhausted.

He did not think that this was the time to raise the controversial issue of artificial or malarial fever. As far as artificial fever in the treatment of neurosyphilis was concerned, he did not think that any comparable series had ever been published in Great Britain ; in the United States of America, the battle was being waged strongly and he had rather thought that the advocates of artificial fever were perhaps a little on top at the moment. After all, one could give artificial fever whenever one liked, as often as one liked, for as long as one liked, as high as one liked, and stop it whenever one liked.

Dr. **Murray Stuart** wished to question Dr. Nicol on one or two points. One was the toxicity of tryparsamide. In his experience it had seemed to be possible to desensitize the patient by giving a small intramuscular injection of tryparsamide and gradually increasing the dose. One man, at about the second or third intravenous injection of tryparsamide, became completely blind and afterwards recovered with equal completeness. The intramuscular dose was gradually increased and he went on quite well afterwards and suffered from no bad effects.

With regard to headaches after lumbar puncture, he had been fairly fortunate. All his patients were treated as out-patients and very rarely complained of headaches. In one case of optic atrophy, however, the ophthalmic surgeon had been impressed by some Russian article to the effect that it was advisable to remove 12 cubic centimetres at one puncture, and in that case a headache did occur after the operation. The speaker had used BAL in 6 cases of dermatitis and all had done extremely well.

Lt.-Col. **R. R. Willcox** said that Dr. Nicol had stated that penicillin was to be used as an adjuvant to malaria. That was one point of view, but others took the view that malaria should be used as an adjuvant to penicillin. In the discussion of Dr. Stokes's own series—a comparable one in size—the opinion was expressed that 4,800,000 units of penicillin by itself was an adequate total course for the majority of cases of neurosyphilis and that the maximum effect would generally be manifest in the first 120 days. He also was of opinion that in the absence of evidence of regression the cases should not be re-tested for a year.

In the United States of America cisternal punctures were being done on an extremely large scale, and it was claimed that patients had no headaches following these ; indeed, the cisternal route was actually preferred to the lumbar route. They were done on an out-patient basis.

Dr. **Forgan** asked whether or not anybody had found arsenoxide in the cerebrospinal fluid at the end of the intensive course.

Dr. **Buckley Sharp** asked whether or not, in the cases of general paralysis of the insane treated with massive doses, any investigation had been made by lumbar puncture of the concentration of penicillin in the cerebrospinal fluid during or at the end of the course. It would be of interest to know how the penicillin worked in these cases, as it did not readily pass the blood-brain barrier. He also desired to ask Dr. Nicol what exactly was an "inactive" fluid as compared with a weakly positive fluid.

Dr. Whelen had started with the hypothesis that any positive changes of the cerebrospinal fluid reaction indicated the existence of living spirochaetes in the central nervous system ; but with malarial infection or malaria-tryparsamide therapy (as they had seen illustrated that day) many patients survived without any further treatment. It seemed to be difficult to imagine that the spirochaetes would die gradually and slowly over so long a period of time. Might not some of the changes persist for a long time after the spirochaetes had all been killed ?

Dr. **W. N. Mascall** said that in his experience the number of complaints about headaches following lumbar puncture had been very small indeed. The test was carried out in the clinic and a large percentage of the patients were sent straight home after the puncture. The ordinary type of needle was employed.

With regard to the use of tryparsamide, in his clinic at one time a number of fatalities had occurred. They therefore limited the course to 10 weekly injections, the total dosage not exceeding 3 grammes. This was followed by 10 weeks of bismuth injections, after which the tryparsamide administration was recommenced.

His experience of the use of BAL was limited. One case of dermatitis treated with this preparation had impressed itself, however, on his mind. The dermatitis had cleared up satisfactorily but was followed by a very severe jaundice. Multiple abscesses then developed, one occurring beneath the scalp. The patient recovered, although she lost all her hair, which, however, had grown again after a considerable lapse of time.

Dr. **Laird** said that Dr. Whelen's paper confirmed the impression which he himself had gained between 1935 and 1938, when he had the opportunity of supervising all the cases of neurosyphilis treated with malaria in Liverpool. Everybody who had spoken in the present discussion had mentioned post-lumbar-puncture headache. Dr. Williams and he shared a common experience. Towards the end of his service career he had experienced a good deal of opposition in the syphilis ward to lumbar punctures. Therefore he had thought that it might be a good idea to change the practice of doing lumbar puncture in the ward itself. Accordingly, he carried out lumbar punctures in a side ward, considerably separated from the syphilis ward, and the patient, on going there, had no idea what the purpose of his going was. The patient had his lumbar puncture, sometimes with the Dattner needle and sometimes with a needle of different bore, and then was told to "carry on". With that procedure there was a very marked decrease in the incidence of post-lumbar-puncture headache, and after having their lumbar puncture patients would indulge in their ordinary activities. There was no correlation between the needles used or between the persons doing the lumbar puncture and the incidence of headache.

Dr. **G. L. M. McElligott,** taking up the point which Dr. Williams had made, agreed that it was probable that some of the cases to which he had referred earlier in the discussion were those of latent acquired infection. However, a considerable proportion of the patients had minor signs

suggestive of a congenital infection, which would have been unnoticed unless one had looked for them specially—for example, gapped teeth and an increased carrying angle of the elbow joints.

Dr. Nicol, replying to the discussion, said that the problem of post-lumbar-puncture headaches had been a very real one in the old days. He had always taught students (and did so still) that if they were going to do lumbar punctures—at any rate so far as neurosyphilis cases were concerned —they should use the Dattner needle and, if necessary, carry out the procedure in the out-patients department. If this fine needle was used patients did not get headaches. Dr. Whelen's practice was to allow the patient to get up and go home within as short a time as a quarter of an hour of the lumbar puncture.

Concerning asymptomatic congenital cases, he wondered how far some of those cases to which the President had alluded were juvenile acquired cases. In the series at Horton Hospital, which extended to over 2,000 cases, he had come across a number in which the syphilis had been acquired when the patient was a juvenile. These patients had fully developed general paralysis of the insane at the age of 25-30 years; this was rather old for the congenital case, although a few cases were undoubtedly congenital. He had felt, however, that some of these were quite possibly acquired cases, and a careful follow-up had often confirmed this suspicion.

Dr. McFarlane had suggested treating these patients with neoarsphenamine to start with and then, if they did not improve, resorting to sterner measures. He agreed, but it had to be remembered that many of the Horton cases had already had a good deal of treatment before admission. In 1937, when Dr. Hutton and he read a paper to the Society, they were absolutely certain that in some of these patients, in spite of receiving regular and constant doses of N.A.B. (neoarsphenamine), general paralysis finally developed.

Dr. Stuart had mentioned the question of desensitizing the patients. He understood that the Americans had done that, but he personally, in the few cases with toxic symptoms, suspended any further treatment with tryparsamide. During the recent war he had seen a paper from the United States of America in which it was noted that the toxicity relative to tryparsamide was very much higher in recent years than it had been 20 years ago, when first employed, and the writer of the paper had raised the question whether there was something in the process of manufacture which made it more toxic.

Returning to the problem of penicillin, at Horton Hospital they had been beginning to use penicillin rather on the lines of those employed at the Naval Auxiliary Hospital at Knowle, giving 300,000 units of penicillin daily up to 4·2 mega units. That course lasted for a fortnight. One or two cases had been tested already in which penicillin had been recovered in the cerebrospinal fluid. No matter what method of treatment was advocated, one must come back to the problem of how far one could treat the patient efficiently in the shortest time. Malaria had been a good therapeutic measure in a number of ways, but if one could bring about better results with penicillin, together with half the amount of malarial fever, and so complete the therapy, so much the better. Some patients were undoubtedly grossly overtreated and that was to be deprecated. If negative reactions could be obtained in two consecutive tests of the cerebrospinal fluid by the use of certain lines of treatment, and if the patient was well and at work, why worry him to continue treatment which was unnecessary?

Dr. Whelen said that there had been one question addressed to her about the length of time that the spirochaete lived after treatment. What she had put forward in her paper was a working hypothesis which, with increased knowledge, might quite well prove to be wrong. On the other hand, if it were assumed that the spirochaetes were killed soon after treatment, what was the explanation of the sero-relapses? Dr. Nicol had referred to the finding of penicillin in the cerebrospinal fluid. At Horton Hospital they were trying the effect of giving penicillin and malaria simultaneously. In the only case which they had so far been able to test, penicillin was found in the cerebrospinal fluid withdrawn one hour after an intramuscular injection of 300,000 units.

She wished to endorse what Dr. Osmond had said about the better outlook for the neurosyphilitic. If the patient came for treatment in time, one could be pretty sure of almost 100 per cent success.

Canadian legislation regarding venereal disease

According to a report in the July 1946 number of the *Canadian Medical Association Journal*, legislation is now in force in the Provinces of Alberta, Saskatchewan, British Columbia, Prince Edward Island and Manitoba requiring a premarital examination of both partners, including a blood test for syphilis, before the issuing of a marriage licence or the publication of banns. The details vary from one Province to another. In Prince Edward Island compulsory submission to treatment is enacted for persons suffering from venereal disease, and wide powers, including the right of search, are given to the Chief Health Officer.